Remarks

Claims 1-12 and 14-56 are pending upon entry of the foregoing amendments.

Amendments to the Claims

Claims 1, 3, 33, and 46 have been amended to specify that the pharmaceutical agent is *dispersed and encapsulated* within the hydrophobic matrix material. That is, the drug is located **not** inside the pores of a microparticles (as taught in the DeLuca patent) but rather is part of the wall structure defining the pores and forming the microparticles. Support for these amendments can be found in the specification, for example, at page 12, lines 15-18.

Rejections under 35 U.S.C. § 112, Second Paragraph

Claim 11 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite. The rejection is respectfully traversed.

The Office Action alleges on page 3 that "[i]t is unclear... what these "derivatives" are (i.e. salts, ester, hydrates, etc.)." Applicants respectfully disagree. "The examiner has the initial burden of presenting by a preponderance of the evidence why a person skilled in the art would not recognize in an applicant's disclosure a description as defined by the claims." In re Wertheim, 541 F.2d 257, 262, 191 U.S.P.Q. 90, 96 (C.C.P.A. 1976); M.P.E.P. § 2163.04. This burden has not been met, because one skilled in the art reading Applicants' specification would undoubtedly recognize a description of the term "derivatives" at page 14, lines 5-8:

> As used herein, "derivatives" include polymers having substitutions, additions of chemical groups, for example, alkyl, alkylene, hydroxylations, oxidations, and other modifications routinely made by those skilled in the art.

Claim 11 is defined sufficiently for one of skill in the art to understand the metes and bounds of the claim with reasonable particularity. The claim therefore comports with the requirements of 35 U.S.C. § 112, second paragraph, and the rejection should be withdrawn.

Rejection under 35 U.S.C. § 103

Claims 1-12 and 14-56 are rejected under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 4,818,542 to DeLuca et al. (hereinafter "DeLuca") in view of U.S. Patent No. 6,395,300 to Straub et al. (hereinafter "Straub"). The rejection is respectfully traversed as applied to the claims as amended.

Applicants' Claimed Formulations and Methods

Applicants' claimed formulations improve the delivery of pharmaceutical agents from microparticles. Specifically, Applicants teach how to select a particular *combination* of microparticle size, porosity, and composition able to release the pharmaceutical agent for a desired sustained period (Pg. 9, Lns. 11-12). The formulations enable one to avoid undesirable burst effects yet can release the majority of the pharmaceutical agent before the microparticles are removed by the pulmonary clearance mechanisms. This advantageously can provide a less fluctuating, more constant concentration of pharmaceutical agent—highly important in the delivery of pharmaceuticals (Pg. 7, Lns. 7-11). The cited prior art, in contrast, does not teach one of ordinary skill in the art how to manipulate the microparticle size, porosity, and composition so as to control the release kinetics of the microparticle matrix material.

DeLuca, alone or in combination with Straub, Teaches Away from Applicants' Claims.

DeLuca discloses a controlled release drug delivery system that includes *pore incorporated* drugs or agents (Abstract). DeLuca does not disclose or teach microparticle drug

formulations in which the pharmaceutical agent *is dispersed and encapsulated within the hydrophobic matrix material.*

DeLuca teaches that "the necessity for biodegradation or bioerosion of the polymer matrix is **obviated** by reason of the intrinsic porosity characteristics of the polymer matrices of the invention and the fact that the **incorporated agent or agents are matrix confined within the interconnecting channels or pores of the spherical polymer.**" (Col. 5, Lns. 15-22) (emphasis added). In other words, the selection of the matrix material would not control the release of pharmaceutical agent because of the pore-incorporated design of the DeLuca formulations. DeLuca teaches that the term "pore incorporated agent" defines "the relative specific location of the agent **confined essentially completely inside the pores** of the porous microspheres of the invention" (Col. 6, Lns. 20-24). The methods for preparing the drug delivery systems create microspheres "wherein the incorporated agent is confined within the walls and channels of the pores as opposed to random distribution within the more poorly defined interstices of the polymer" (Col. 6, Lns. 15-19). Therefore, DeLuca teaches that **the drug agent** is **not part of the structure of the wall forming material, but rather is confined to the interior surface of the pores or channels in the structure**. In contrast, the formulations and methods of Applicants' independent claims 1, 3, 31, and 46 are designed so that the drug release profile depends *inter alia* on the selection of the matrix material.

Furthermore, DeLuca does not teach Applicants' claimed release profile, and does not teach how to select the combination of the pharmaceutical agent, matrix material, geometric size, and average porosity to control release rate.

DeLuca Fails to Inherently Disclose Applicants' Claimed Release Profile

The Examiner's rejection is premised upon the notion that Applicants' claimed release profile is inherent in the formulation disclosed in DeLuca. Specifically, the Examiner states that "any porous microparticle having the claimed drug and matrix material would have the release profile as claimed." (Office Action, page 6). Applicants' respectfully disagree.

A claim element is not "inherent" in the disclosure of a prior art reference unless **extrinsic evidence** clearly shows that missing descriptive matter is **necessarily** present in the thing described in the reference. In re Robertson, 49 U.S.P.Q. 1949 (Fed. Cir. 1999). "Inherency, however, may not be established by mere probabilities or possibilities" (49 U.S.P.Q. at 1950-51). The sole "evidence" relied on by the Examiner is that "there is no additional information in the specification with regards to the release profile (i.e. coating or physical makeup which makes it a sustained release)." This is not evidence of anything other than mere possibility. Because the structure of the drug/matrix material in DeLuca differs from that of Applicants' claims (as described above), the evidentiary burden remains with the Examiner.

The Examiner posits, wholesale and without proof, that DeLuca's pore confined drug would be delivered with equivalent kinetics of release as Applicants' microparticles. This is legally insufficient to support the rejection.

Applicants' claims are enabled by selection of a particular *combination* of particle size, porosity, and composition. Contrary to the Examiner's assertion, detailed information regarding the physical makeup that allows Applicant's methods and formulations to achieve the claimed release profile can be found, for example, at page 7, lines 7-20 and page 10, lines 14-24:

> ... it has been discovered that the composition of the microparticles (e.g., the matrix material, surfactant) can be selected to provide delayed release (and avoid the burst effect associated with immediate release formulations), and the porosity of the microparticles can be selected to provide the majority of the pharmaceutical agent release before the microparticles are removed by the pulmonary clearance mechanisms. Although the composition of the microparticles can be selected to slow the release of the pharmaceutical agent, selection of the composition alone may not ensure that a sufficient amount of pharmaceutical agent is released before the microparticles are removed by the pulmonary clearance mechanisms. For a given composition of the microparticles, the porosity can be selected to ensure that a therapeutically or prophylactically effective amount of the pharmaceutical agent continues to be released after 2 hours, preferably such that a majority (e.g., more than 50%, more than 75%, more than 90% by weight of the pharmaceutical agent) of the pharmaceutical agent is released from the microparticles by 24 hours following inhalation.
>
> ....
>
> For a given microparticle composition (pharmaceutical agent and matrix material) and structure (microparticle porosity and thus density) an iterative process can be used to define where the microparticles go in the lung and the duration over which the microparticles release the pharmaceutical agent: (1) the matrix material, the pharmaceutical agent content, and the microparticle geometric size are selected to determine the time and amount of initial pharmaceutical agent release; (2) the porosity of the microparticles is selected to adjust the amount of initial pharmaceutical agent release, and to ensure that significant release of the pharmaceutical agent occurs beyond the initial release and that the majority of the pharmaceutical agent release occurs within 24 hours; and then (3) the geometric particle size and the porosity are adjusted to achieve a certain aerodynamic diameter which enables the particles to be deposited by inhalation to the region of interest in the lung.

In contrast, DeLuca fails to provide one of ordinary skill in the art with the necessary tools to select an appropriate combination of porosity, particle size and composition to produce

porous microparticles of pharmaceutical agent and a hydrophobic matrix material, wherein, upon inhalation of the formulation into the lungs, a therapeutically or prophylactically effective amount of the pharmaceutical agent is released from the microparticles in the lungs for at least 2 hours.

Applicants' Claimed Formulations and Methods are Non-Obvious over DeLuca

The rejection appears premised upon the notion that one of ordinary skill in the art would look to DeLuca to optimize a microparticle formulation. Page 6 of the Office Action states that it would be obvious to determine the amount of pores necessary to achieve the release profile as claimed. Applicants' respectfully disagree because it would have required more than ordinary skill to derive Applicants' claimed formulations for sustained release from the teachings of DeLuca.

Obviousness requires more than a mere suggestion of trying to solve the same problem, particularly where there are a myriad of possible paths to explore for the solution. A person of ordinary skill in the art trying to alter the release profile—the problem posited by the Examiner—has numerous technical options to choose from in trying to meet such an objective. For example, DeLuca teaches that the matrix may be coated with a film or cross-linking agent to inhibit or control release rates (Col. 5, Lns. 24-26 and 30-34). In contrast, Applicants' claimed methods and compositions for achieving sustained release are enabled by selection of a particular *combination* of particle size, porosity, and composition. Therefore, one of ordinary skill in the art would not have been led to derive Applicants' claimed methods and formulations. Motivation to achieve a particular result should not be confused with a teaching of *how* to achieve that result.

Applicants' Claimed Formulations and Methods Are Non-obvious

Over DeLuca in Combination with Straub

In contrast with Applicants' claimed methods and formulations, which use *hydrophobic* matrix material to *delay* drug release, Straub discloses that drugs, especially low aqueous solubility drugs, can be provided in microparticles so as to *enhance* the dissolution of the drug (Abstract). As discussed in the previous response, Straub teaches away from Applicants' claimed methods and formulations, because Straub teaches the use of the *hydrophilic* matrices materials in order to *increase* drug release.

The Examiner's rejection is premised upon the notion that "Straub et al.... teach that excipients such as bulking agents can be added to the composition of DeLuca." (Pg. 6). The Office Action states that "[t]herefore, when looking for examples of excipients that can be used in porous microparticles, one of ordinary skill in the art could look to Straub et al. which teach a porous microparticle composition." (Pg. 6). Applicants' respectfully disagree.

When applying 35 U.S.C. § 103, "the following tenets of patent law must be adhered to: (A) The claimed invention must be considered as a whole; (B) The references *must be considered as whole* and must suggest the desirability and thus the obviousness of making the combination." Hodosh v. Block Drug Co., 786 F.2d 1136, 1143 n. 5 (emphasis added). Furthermore, "[a]ll evidence bearing on the issue of obviousness... must be considered and evaluated **before** the required legal conclusion is reached. W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 1555. Thus, "[a] prior reference must be considered in its entirety, i.e. as a whole, **including portions that would lead away from the claimed invention**." M.P.E.P. § 2141.02 [VI] (emphasis added).

One of ordinary skill in the art would undoubtedly understand that Straub *when read as a whole* teaches that it is undesirable to use *hydrophobic* matrix materials for *immediate* drug release. As Straub teaches the use of *hydrophilic* matrices materials in order to *increase* drug release, one of ordinary skill would not have had any reason to combine DeLuca and Straub to derive Applicants' pulmonary drug formulations (which comprise a pharmaceutical agent and *hydrophobic* matrix material) and methods for releasing a majority of the pharmaceutical agent before the inhaled microparticles are removed by the pulmonary clearance mechanisms, while also avoiding undesirable burst effects associated with conventional immediate release formulations.

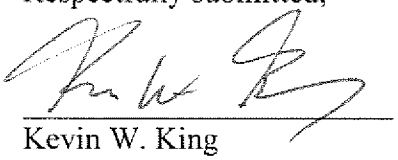
It is improper for the Examiner to ignore evidence that Straub as a whole teaches away from Applicants' claimed invention, yet selectively parse the same document to support a rejection. Accordingly, no *prima facie* case of obviousness has been established for the present claims.

Conclusions

For the foregoing reasons, Applicants submit that the claims are patentable over the prior art of record. Allowance of claims 1-12 and 14-56 is therefore respectfully solicited.

The undersigned respectfully invites the Examiner to contact him by telephone (404.853.8068) if any outstanding issues can be resolved by conference or examiner's amendment.

Respectfully submitted,



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